CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number NDA 21-310

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-310 / N-000	Brand Name	Alora® TD system
OCPB Division (I, II, III)	DPE2	Generic Name	Estradiol transdermal system
Medical Division	DMEDP	Drug Class	
OCPB Reviewer	Robert Shore, Pharm.D.	Indication(s)	Prevention [redacted] of PMO.
OCPB Team Leader	Hae-Young Ahn, Ph.D.	Dosage Form	Transdermal system
		Dosing Regimen	0.025 mg/day applied twice weekly
Date of Submission	12-JAN-01	Route of Administration	topical
Estimated Due Date of OCPB Review	10-SEP-01	Sponsor	Watson Laboratories, Inc., Salt Lake City, Utah
PDUFA Due Date	16-NOV-01	Priority Classification	3S
Division Due Date	09-OCT-01		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE	[redacted]	[redacted]	[redacted]	[redacted]
Table of Contents present and sufficient to locate reports, tables, data, etc.	X	[redacted]	[redacted]	
Tabular Listing of All Human Studies	X	[redacted]	[redacted]	
HPK Summary	X	[redacted]	[redacted]	
Labeling	X	[redacted]	[redacted]	
Reference Bioanalytical and Analytical Methods	X	[redacted]	[redacted]	[redacted] included
I. Clinical Pharmacology	[redacted]	[redacted]	[redacted]	[redacted]
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	[redacted]	[redacted]	[redacted]	[redacted]
Healthy Volunteers-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:				
Patients-	[redacted]	[redacted]	[redacted]	[redacted]
single dose:				
multiple dose:	X	1		
Dose proportionality -	[redacted]	[redacted]	[redacted]	[redacted]
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	X	1		
Drug-drug interaction studies -	[redacted]	[redacted]	[redacted]	[redacted]
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				

Dose stays in Appro

[redacted]

Analytic method. RIA

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In-vitro:				
Subpopulation studies -	[redacted]	[redacted]	[redacted]	[redacted]
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 2:				
Phase 3:				
PK/PD:	[redacted]	[redacted]	[redacted]	[redacted]
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	1		
Population Analyses -	[redacted]	[redacted]	[redacted]	[redacted]
Data rich:				
Data sparse:				
II. Biopharmaceutics	[redacted]	[redacted]	[redacted]	[redacted]
Absolute bioavailability:				
Relative bioavailability -	[redacted]	[redacted]	[redacted]	[redacted]
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	[redacted]	[redacted]	[redacted]	[redacted]
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies	[redacted]	[redacted]	[redacted]	[redacted]
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	[redacted]	1		

Alora® 0.05, 0.075, and 0.1 mg/day transdermal systems are approved under NDA 20-655 for: Treatment of moderate-to-severe vasomotor symptoms associated with the menopause; Treatment of vulval and vaginal atrophy, and; Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. NDA 21-310/N-000 seeks approval of Alora® 0.025 mg/day for the prevention [redacted] of postmenopausal osteoporosis.

One study has been submitted to section 6. Protocol 1996023 was a phase 3, 24 months' duration, dose-ranging clinical study in which PMO women were treated with either one of three Alora® TD systems or a placebo TD system. Pharmacokinetic samples for serum estradiol determination were obtained at baseline and after 12, 18, and 24 months of

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treatment. The pharmacokinetic analysis of this clinical study as well as an Emax model relating serum estradiol concentrations to absolute changes in bone mineral density have been submitted in Section 6.

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?	None at this time	
QBR questions (key issues to be considered)	• Is the lower strength 0.025mg/day system dose proportional to the higher approved strengths? • Are the pharmacokinetics and pharmacodynamic related?	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

CC: NDA 21-310/N-000, HFD-850(Electronic Entry or Lee), HFD-510(Hedin), HFD-870(Ahnh, Malinowsky, Hunt), CDR.

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OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-310	Submission Date(s): 16-Jan-01
Brand Name	Alora®
Generic Name	Estradiol Transdermal Systems
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn
OCPB Division	DPE II
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Watson Laboratories, Inc., 417 Wakara Way, Salt Lake City, Utah 84108
Submission Type	Original NDA
Related NDA	NDA 20-655
Formulation; Strength(s)	Transdermal Patch; 0.025, 0.05, 0.075 and 0.1 mg/day
Indication	Prevention [redacted] of postmenopausal osteoporosis

I. Executive Summary

Watson Laboratories, Inc. submitted an NDA 21-310 for four strengths (surface areas) of Alora® Estradiol Transdermal System (EMTDS), 0.025 mg/day (9 cm^2), 0.05 mg/day (18 cm^2), 0.075 mg/day (27 cm^2), and 0.1 mg/day (36 cm^2) on 16-Jan-01.

Presently, three dosage strengths of Alora®, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are marketed in accordance with NDA 20-655 that was approved by the Division of Reproductive and Urologic Drug Products for the treatment of moderate to severe vasomotor symptoms associated with menopause.

This application provided a clinical trial to support an additional indication of prevention [redacted] of postmenopausal osteoporosis for currently marketed dosage strengths of Alora®, as well as related information to support a new 0.025 mg/day dosage strength for the osteoporosis indication. The new low dosage strength has an identical formulation to the currently approved strengths and differs only with respect to its surface area.

A. Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-310 submitted on 16-Jan-01. The overall Human Pharmacokinetic Section is acceptable to OCPB. Labeling comments outlined in the labeling section of the review should be conveyed to the sponsor as appropriate.

Wei Qiu, Ph.D.
Division of Pharmaceutical Evaluation II

Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by Hae-Young Ahn, Ph.D., Team Leader

FT initialed by Hae-Young Ahn, Ph.D., Team Leader

DFS CODE: AP

II. Table of Contents

III. Summary of CPB Findings

Dose proportionality of the 0.025 mg/day, 0.05 mg/day and 0.075 mg/day strengths was assessed by measuring serum estradiol concentrations in the study population participating in a placebo-controlled safety and efficacy study in osteoporosis (Protocol 1996023). Serum samples were collected at a pre-treatment and at the end of 12 months (Cycle 13), 18 months (Cycle 20), and 24 months (Cycle 26) of treatment and analyzed for estradiol using

The mean (SD) uncorrected and baseline-corrected steady-state serum estradiol concentrations, average for Cycles 13, 20, and 26, are provided in **Table 1**.

Table 1. Steady-State Serum Estradiol Concentrations (pg/ml) for the Placebo and Alora® Treatments

Treatment	Uncorrected	**Baseline-Corrected**
Placebo	9.3 (8.80)	3.2 (8.62)
Alora 0.025 mg/day	24.5 (12.35)	18.6 (12.17)
Alora 0.05 mg/day	42.6 (23.67)	35.9 (23.78)
Alora 0.075 mg/day	56.7 (36.78)	50.1 (36.07)

Dose proportionality was evaluated using the weighted regression approach. The results of the weighted regression analysis indicated that the average baseline-corrected steady-state serum estradiol concentrations were proportional for systems with delivery rates of 0.025 to 0.075 mg/day.

The relationship between serum estradiol concentrations and the changes in bone mineral

density at 1 and 2 years was investigated using an Emax model. The mean (SD) % changes in bone mineral density at 1 and 2 years during treatment with placebo and the 3 strengths of Alora® are provided in **Table 2.**

Table 2. Mean (SD) % Changes in Bone Mineral Density at 1 and 2 years during Treatments with Placebo and Alora Systems

Treatment	1 Year	2 Year
Placebo	-0.06 (0.50)	-0.59 (0.53)
Alora 0.025 mg/day	1.43 (0.42)	1.65 (0.59)
Alora 0.05 mg/day	3.52 (0.53)	4.08 (0.47)
Alora 0.075 mg/day	4.34 (0.46)	4.82 (0.61)

These data indicated an overall relationship between increased bone mineral density at 1 and 2 years and increasing dose regarding to the mean values. However, the model that was fitted to the individual data at 2 years had low coefficients ($r^2 = 0.486$) of determination indicating a lack of correlation between change in bone mineral density and estradiol concentrations. (**Figure 1**).

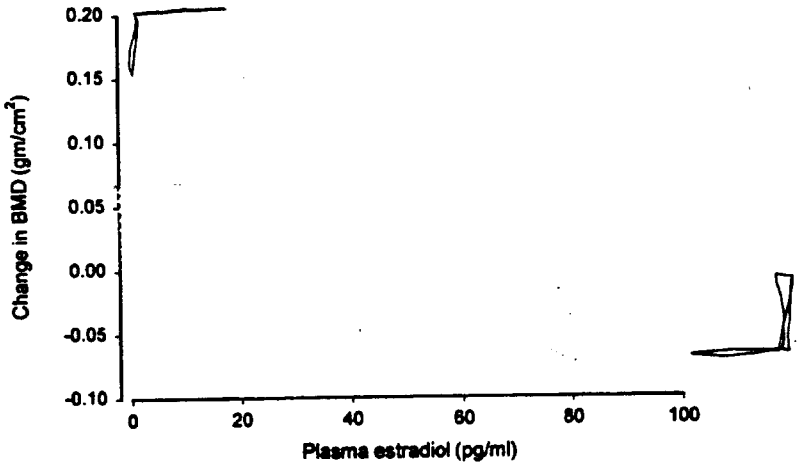

Figure 1. Agreement between the Observed Data and the Fitted Emax Function for Changes in Bone Mineral Density Data

IV. QBR

A. General Clinical Pharmacology

Q. What is the basis for selecting BMD as a biomarker?

Osteoporosis is a metabolic bone disease that affects mainly the elderly. Estrogen deficiency resulting from menopause leads to an earlier onset of the disease in women compared to men. Particularly striking is the rapid decline in bone mineral density (BMD) seen in predominantly

cancellous bone found in the vertebrae. The progressive loss of bone mass eventually leads to fracture that is the clinical endpoint for osteoporosis.

Q. What is the dose-concentration relationship?

Previously, the dose proportionality of the strengths 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day (E94004) was assessed. It was pointed out previously (NDA 20-655 review) that strict dose proportionality between the three systems was not observed due to the large variability in estradiol pharmacokinetics and baseline (endogenous) estradiol.
In this application, dose proportionality of the strengths 0.025 mg/day, 0.05 mg/day and 0.075 mg/day was evaluated in a Phase III clinical trial (Protocol 1996023). Study 1996023 was a double-blind, double-dummy, randomized, placebo-controlled, parallel, multi-center, dose-ranging study of 24 months' duration in postmenopausal women. Patients were assigned to one of the following 4 treatment groups according to a previously established randomization code: (1) Estradiol 0.025 mg/day (9 cm^2 system) and placebo (18 cm^2 system); (2) 0.05 mg/day (18 cm^2 system) and placebo (9 cm^2 system); (3) 0.075 mg/day (18 cm^2 and 9 cm^2 active systems); or (4) placebo (18 cm^2 and 9 cm^2 placebo system). Each system was worn for about 3.5 days. Each 28-day treatment was referred to as a cycle. Each patient was to undergo 26 consecutive cycles during this 2-year study.

Serum was harvested from blood samples collected prior to the start of treatment, and after 12, 18, and 24 months of treatment. These assessment times corresponded to the end of Cycles 13, 20, and 26, respectively. Blood samples were collected at any time within the 3.5-day interval. The time of blood collection and the date and time of application of the last system were recorded to permit calculation of the interval between system application and blood sampling. Serum samples were analyzed for estradiol using _____

analytical method

A total of 355 patients were enrolled into this study. Data from 34 of the patients were excluded from the analysis because one or both systems were not adhered at the time of blood sampling, the interval between system application and blood sampling exceeded 100 hour, or the patients were taking additional forms of estrogen replacement therapy at the time of blood sampling. A total of 321 patients had serum estradiol concentration data at baseline.

Statistical comparison of the baseline-adjusted serum estradiol concentrations on the first, second, third and fourth day of application did not identify any significant differences ($p>0.05$) between application days for any of the treatment groups. The differences in paired baseline adjusted serum estradiol concentrations at Cycle 13 and Cycle 20, and Cycle 13 and Cycle 26 were not statistically significant ($p>0.05$) for any of the treatment groups. The steady-state was attained by Cycle 13 and sustained to Cycle 26 for baseline-adjusted estradiol concentrations. The mean (SD) serum estradiol concentrations for the placebo and 3 Alora treatments in the prevention of osteoporosis trial are given in **Table 4**. The numbers of patients who contributed to the mean calculations are shown as well.

Table 4. Mean (SD) Serum Estradiol Concentrations at Baseline and During Treatments with Placebo and Alora Systems

Time	Descriptive Statistic	Placebo	Alora 0.025 mg/day	Alora 0.050 mg/day	Alora 0.075 mg/day
Baseline	Mean (SD)	6.3 (2.82)	6.4 (3.10)	6.7 (3.73)	6.6 (3.62)
	Number of Patients	79	81	78	83
Cycle 13	Mean (SD)	8.7 (6.98)	25.0 (11.49)	40.5 (22.58)	54.9 (32.74)
	Number of Patients	59	45	47	46
Cycle 20	Mean (SD)	8.2 (3.45)	24.6 (11.64)	42.5 (19.84)	61.9 (33.92)
	Number of Patients	50	41	44	40
Cycle 26	Mean (SD)	10.9 (12.71)	23.8 (14.23)	45.0 (28.11)	53.8 (42.94)
	Number of Patients	58	38	45	45

According to the sponsor, a test for overall dose proportionality of average, baseline-adjusted, steady-state serum concentrations for each individual patient was performed using the weighted regression approach. The quadratic term, c, in the following equation was tested to determine if it differed significantly from zero:

$Y = a + b(dose) + c(dose^2)$

where Y was the mean estradiol concentration at steady state (Cycles 13, 20, and 26) for each individual patient. Similarly, the intercept term, a, in the following equation also was tested to determine if it differed significantly from zero:

$Y = a + b(dose)$

The results of the statistical analysis of the average baseline-adjusted steady-state serum concentration data are summarized in **Table 5.**

Table 5. Weighted Regression Analysis of the Dose Proportionality Data in the Evaluable Population

Test	Variable	Parameter Estimate	SE	P-value	Conclusion
Step 1: Test for Linearity	a	1.32	11.06	0.9049	Linearity Achieved
	b	0.65	0.54	0.2300	
	c	0.00	0.01	**0.9943**	
Step 2: Test for Dose Proportionality	a	1.40	3.54	**0.6934**	Dose Proportionality Achieved
	b	0.65	0.08	0.0001	

The results showed that both the coefficient of the quadratic term, c, and the intercept term, a, were not significantly different from zero ($p>0.05$), indicating that serum estradiol concentrations were dose proportional for systems with delivery rates of 0.025 to 0.075 mg/day.

Q. What are the characteristics of the exposure-response relationships for efficacy?

The decline in endogenous estradiol production that occurs at menopause leads to an accelerated loss in bone mineral density and to the development of postmenopausal osteoporosis. The relationship between the average, baseline-adjusted, steady-state serum concentration (C) and absolute changes in bone mineral density (R) was investigated using the Emax model.

$R = Emax \cdot C/(C_E50 + C) + PR$

Where Emax was the maximum response achieved, C_E50 was the serum concentration producing 50% of the maximum effect, and PR is the placebo response. The placebo response, PR, was set as a fixed variable equal to the average change in bone mineral density for the placebo group only (PR = -0.0053).

The mean (SD) % changes in bone mineral density at 1 and 2 years during treatment with placebo and the 3 strengths of Alora are provided in **Table 2.** These data indicate a dose-response relationship in the mean data at 1 and 2 years. Non-linear regression results for the Emax model are given in **Table 6.**

Table 6. Non-Linear Regression Results of Emax Model (Evaluable Population)

Dependent Variable	Parameter	Estimate	SE	95% CI	p-value	Model R^2
Change in Bone Mineral Density (g/cm^2)[a]	Emax	0.0610	0.0122	(0.0368, 0.0852)	< .001	**0.49**
	C_E50	11.9063	8.5573	(-5.0235, 28.8361)		

[a]. Note that SE and 95% CI were based on asymptotic variances from non-linear regression approach.

The model that was fitted to the individual data at 2 years had low coefficients of determination indicating a lack of correlation between change in bone mineral density and doses.

B. General Biopharmaceutics

Q. Are the 0.025 mg/day strength batches used in the clinical trial bioequivalent to the to-be-marketed products?

The comparison between the 0.025 mg/day strength batches used in the osteoporosis study (Protocol no. 1996023) and to-be-marketed products is given in Table 3. The [redacted] were used in clinical trial batches (96Z163 and 97Z184) and to-be-marketed products, respectively. The Alora

[redacted]

Table 3. Comparison between System used in Phase III Osteoporosis Clinical Study No. 1996023 and To-Be-Marketed Products

Component	Solution Percent by Weight		Note
	Target (%)	Range (%)	
Estradiol, USP	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	Clinical Trial Batches (96Z163 and 97Z184) used [redacted] To-Be-Marketed Products used [redacted]
Sorbitan MonoOleate, NF	[redacted]	[redacted]	
Total	[redacted]		

The 0.025 mg/day strength used in the clinical trial are considered to be bioequivalent to those to-be-marketed products based on two reasons although a formal BE trial has not been conducted.

First, the drug substance, components, and quantitative composition of the estradiol transdermal system, 0.025 mg/day strength, are identical to the currently approved dosage strengths with the exception of the system size.
Secondly, it has been shown that the 0.05 mg/day strength manufactured with the [redacted] (clinical) and [redacted] (to-be-marketed) versions of the [redacted] were bioequivalent

Trade Secret

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	October 19, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 417 Wakara Way, Salt Lake City, Utah 84108	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Estra-1,3,5 (10)-triene-3, 17-diol	None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☒ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora

This application contains the following items: *(Check all that apply)*

☐	1. Index	
☐	2. Labeling *(check one)*	☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☒	4. Chemistry section	
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☐	16. Debarment certification (FD&C Act 306(k)(1))	
☐	17. Field copy certification (21 CFR 314.50(k)(3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. Financial Information (21 CFR Part 54)	
☐	20. OTHER *(Specify)*	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Executive Director, Regulatory Affairs	October 19, 2001
ADDRESS *(Street, City, State, and ZIP Code)* 417 Wakara Way Salt Lake City, Utah, 84108		TELEPHONE NUMBER (801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

WATSON Laboratories, Inc.

DUPLICATE

A Subsidiary of Watson Pharmaceuticals, Inc. N-000-BL

May 11, 2001

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day
Revised labeling

Dear Dr. Jenkins:

Reference is made to the telephone conversation on May 2, 2001 between Randy Hedin from DMEDP and Dorothy Frank from Watson Laboratories, Inc. During this conversation, Mr. Hedin requested an electronic copy of the labeling in Microsoft Word and requested that Watson amend the labeling to include only the changes related to the osteoporosis indication. Mr. Hedin said that the additional changes made to the label unrelated to the osteoporosis indication could not be reviewed by DMEDP, and that they should be submitted to DRUDP for consideration. As requested enclosed with this submission are the following items:

- Amended Package Insert
- Annotated Package Insert showing the changes from the current commercial label
- Amended Patient Information Leaflet
- Annotated Patient Information Leaflet showing the changes from the current commercial label
- CD-ROM containing electronic copies of the labeling

If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	May 11, 2001
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number (Include Area Code)**
(801) 588-6200	(801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Estra-1,3,5 (10)-triene-3, 17-diol	None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION To provide revised draft labeling

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora

This application contains the following items: *(Check all that apply)*

☒	1. Index	
☒	2. Labeling *(check one)*	☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))	
☐	4. Chemistry section	
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)	
☐	B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)	
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)	
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)	
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)	
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))	
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)	
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)	
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)	
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)	
☐	12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)	
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))	
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A)	
☐	15. Establishment description (21 CFR Part 600, if applicable)	
☐	16. Debarment certification (FD&C Act 306(k)(1))	
☐	17. Field copy certification (21 CFR 314.50(k)(3))	
☐	18. User Fee Cover Sheet (Form FDA 3397)	
☐	19. Financial Information (21 CFR Part 54)	
☐	20. OTHER *(Specify)*	

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	May 11, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

DUPLICATE

WATSON
Laboratories, Inc.
A Subsidiary of Watson Pharmaceuticals, Inc.

May 11, 2001

N 000 SU
ORIG AMENDMENT

John K Jenkins, M.D., Director
Division of Metabolic and
Endocrine Drug Products, HFD 510
Center for Drug Evaluation and Research
Document Room 14B-10
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA #21-310**: Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day
Amendment – 120 day safety report

Dear Dr. Jenkins:

In accordance with 21 CFR 314.50(d)(5)(vi)(b) and section 505(i) of the act, Watson Laboratories, Inc. is submitting this correspondence to fulfill the requirement for submission of a 120-day Safety Update for **NDA #21-310.**

There is no new safety information regarding this product.

If you have any questions or comments regarding the information provided, please do not hesitate to contact me by phone (801) 588-6200 or fax (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Research Park, 417 Wakara Way, Salt Lake City, UT 84108 • Tel: 801/588-6200 • Fax: 801/583-6042

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

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APPLICANT INFORMATION

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(801) 588-6200	(801) 583-8135
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417 Wakara Way Salt Lake City, Utah 84108	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION 120 day safety report

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
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Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50(c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* 120 day safety report

CERTIFICATION

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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
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The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

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SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Cheri L. Peterson for D. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	May 11, 2001

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah, 84108	(801) 588-6200

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)artment of Health and Human Services
)d and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

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ORIGINAL

WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

February 14, 2000

John K. Jenkins, M.D., Director
Division of Metabolic and Endocrine
Drug Products (HFD- 510)
CDER, Document Room 14-B-19
U.S. Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-310 Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

Dear Dr. Jenkins:

In accordance with the Federal Food, Drug, and Cosmetic Act, Watson Laboratories, Inc. is submitting an amendment to our New Drug Application for a new system size and indication for Alora Estradiol Transdermal Systems. Alora is also subject of our NDA —— that was reviewed and approved by the Division of Reproductive and Urologic Drug Products. Three dosage strengths, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day are approved in NDA —— for the treatment of moderate to severe vasomotor symptoms associated with menopause.

This amendment is submitted to withdraw the words ———— from the indication proposed in our original submission for 0.025 mg/day, 0.05 mg/day, 0.075 mg/day, and 0.1 mg/day Alora Estradiol Transdermal Systems. The new proposed indication is "prevention of postmenopausal osteoporosis".

If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Sincerely,

Dorothy A. Frank, M.S., R.A.C.
Director, Regulatory Affairs

Desk copy: Randy Hedin

REVIEWS COMPLETED | S
CSO ACTION
LETTER | N.A.I. | MEMO
CSO INITIALS | DATE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Watson Laboratories, Inc.	February 14, 2003
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Estradiol Transdermal System (EMTDS)	Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5(10)-triene-3,17-diol — CODE NAME *(If any)* None

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Transdermal System	0.025, 0.05, 0.075 and 0.1 mg/day	Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION To revise indication

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED — THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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See attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-555 Alora

This application contains the following items: *(Check all that apply)*

- ☐ 1. Index
- ☐ 2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
- ☐ 3. Summary (21 CFR 314.50(c))
- ☐ 4. Chemistry section
  - ☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - ☐ B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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- ☐ 18. User Fee Cover Sheet (Form FDA 3397)
- ☐ 19. Financial Information (21 CFR Part 54)
- ☒ 20. OTHER *(Specify)* Te revise indication

CERTIFICATION

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5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Dorothy A. Frank for D. Frank	Dorothy A. Frank, M.S., R.A.C. Director, Regulatory Affairs	[illegible]

ADDRESS *(Street, City, State, and ZIP Code)*	TELEPHONE NUMBER
417 Wakara Way Salt Lake City, Utah 84108	[illegible]

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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Draft

Labeling

MEMORANDUM

Re: NDA 21-310, Alora Estradiol Transdermal System, Final Labeling

Date: April 4, 2002

Referenced Document: Response to Approvable Letter, February 5, 2002, N000 AL.

Medical Officer: Patricia R. Beaston-Wimmer, M.D., Ph.D.

Medical Team Leader: Eric Colman, M.D.

The revised proposed label has been reviewed in full. Watson has incorporated the suggestions from this Medical Reviewer into the osteoporosis section. The changes made in reference to the indication for postmenopausal osteoporosis are acceptable.

The remainder of the label has been negotiated with the Division of Urologic and Reproductive Drug Products (HFD-580).

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Patricia Beaston-Wimmer
4/4/02 02:25:46 PM
MEDICAL OFFICER

Eric Colman
4/8/02 08:34:37 AM
MEDICAL OFFICER

DUPLICATE

WATSON
Laboratories, Inc.

A Subsidiary of Watson Pharmaceuticals, Inc.

16 October, 2001

Division of Metabolic and Endocrine Drug Products (HFD- 510)
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Document Room 14-B-19
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMEN

RE: NDA 21-310, Alora® Estradiol Transdermal System, 0.025 mg/day, 0.05 mg/day, 0.075 mg/day and 0.1 mg/day

In response to telephone inquiries on October 1 and 4 of this year by Dr. Wei Qiu regarding the biopharmaceutical review of NDA 21-310, we are providing the following clarifying information, and amending the proposed labeling. The details are provided below.

A. Dr. Qiu requested clarification regarding the calculations in Table 4 (page 27 in volume 6.01 of the NDA). In response to that question, we are providing herewith an amended copy of Table 4 (the values have not changed, but a typographical error was corrected in Step 1: the description of variable "c" was "Dose", when it should have been "Dose^2". Dr. Qiu also inquired about the value of 0.65 reported for "Dose" (slope) shown in Step 2; we are providing the following explanation for that value:

   In the analysis of the dose proportionality data we did not attach any significance to the numerical value of the slope but simply tested to see if the coefficient of the quadratic term in the quadratic equation and the intercept in the linear equation were significantly different from zero. In Table 4 the dose (or more accurately the daily rate) was expressed in μg/day hence the value of 0.65 but the units in this case do not make a great deal of sense (i.e. $pg \cdot ml^{-1} \cdot \mu g^{-1} \cdot day$). Using the same mass units, the slope value (which essentially represents 1/clearance) would be 6.5×10^{-7} $ml^{-1} \cdot day$. The clearance value calculated from the slope is 64.1 L/hr which is in close agreement with the values estimated from other studies (see: Draft Labeling, Table 1).

B. Dr. Qiu inquired regarding the source of the data, in Table 2 of the proposed insert, labeled as "Study 1" and "Study 2". Watson's response follows:

   Studies 1 and 2 in Table 2 refer to Protocols E94001 and E94002, respectively, that were included in the original NDA for Alora in the treatment of menopausal symptoms (NDA 20-655). The values reported for the two studies were derived from the individual serum level data listed in the Pharmacokinetic Section of NDA 20-655 in Volume XXV (Study 1; Protocol E94001; Appendix C) and Volume XXVI (Study 2: Protocol E94002; Appendix C). With the addition of the new strength of Alora it was believed that this data presented in a tabular format would add clarity to the

pharmacokinetics and delivery of estradiol from the different available dosage strengths.

C. The proposed insert contains, directly under Figure 3, the statement,

[ ]

Ms. Qiu requested clarification of the source of the number

The number — was incorrectly transcribed from an earlier draft report for evaluable subjects, and has now been corrected to — subjects. This number represents the number of evaluable patients in the study.

After careful consideration we would propose the following change to the draft labeling, to more clearly and accurately represent the data referring to dose proportionality (under Figure 3):

[ ]

We trust this provides sufficient clarification of Dr. Qiu's questions to permit continued review of this NDA. If you have any questions or need any additional information, please feel free to contact me by telephone at (801) 588-6200 or by fax at (801) 583-8135.

Best Regards,

Dorothy A. Frank

Dorothy A. Frank, M.S., R.A.C.
Executive Director, Proprietary Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT Watson Laboratories, Inc.	DATE OF SUBMISSION October 16, 2001
TELEPHONE NO. (Include Area Code) (801) 588-6200	FACSIMILE (FAX) Number (Include Area Code) (801) 583-8135
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*: 417 Wakara Way Salt Lake City, Utah 84108	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-310

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* Estradiol Transdermal System (EMTDS)

PROPRIETARY NAME *(trade name)* IF ANY Alora® Estradiol Transdermal System

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* Estra-1,3,5 (10)-triene-3, 17-diol

CODE NAME *(If any)* None

DOSAGE FORM: Transdermal System

STRENGTHS: 0.025, 0.05, 0.075 and 0.1 mg/day

ROUTE OF ADMINISTRATION: Transdermal

(PROPOSED) INDICATION(S) FOR USE: Treatment of moderate-to-severe vasomotor symptoms associated with menopause. Treatment of vulval and vaginal atrophy. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure. Prevention of postmenopausal osteoporosis.

APPLICATION INFORMATION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION Response to Request for Information

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g., Final dosage form, Stability/testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See Attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA #20-655 Alora

with respect to the rate and extent of estradiol delivery after single application of the respective systems to the lower abdomen of healthy postmenopausal women. The sponsor received approval to use [redacted] in April 1998 (supplemental filing NDA 20-655/S-002).

Analytical
All
Redacted
- OJT

C. Analytical

Q. What was the bioanalytical method used to assess serum estradiol concentrations? Has the assay method adequately validated?

[redacted]

V. Labeling

(~~Strikeout text~~ should be removed from labeling; Double <u>underlined text</u> should be added to labeling; ☞ indicates an explanation only and is not intended to be included in the labeling)

Pharmacokinetics

[redacted]

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Draft

Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Wei Qiu
1/16/02 11:31:09 AM
PHARMACOLOGIST

Hae-Young Ahn
1/16/02 11:50:48 AM
BIOPHARMACEUTICS